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### THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and  
provisional Specification filed on 17/04/2003 in respect of Patent Application No.384/MUM/2003 of (a)  
Mr. IPCA LABORATORIES LIMITED, (b) 48, Kandivli Industrial Estate, Mumbai - 400 067,  
Mumbai, Maharashtra, India (c) Indian company incorporated under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act,

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Dated this 5<sup>th</sup> day of October 2006.

M.A. Haafeez  
(M.A. HAAFEEZ)  
ASSTT.CONTROLLER OF PATENTS & DESIGNS

CERTIFIED COPY OF  
PRIORITY DOCUMENT

**FORM 1**

**THE PATENTS ACT, 1970**  
(39 of 1970)

**APPLICATION FOR GRANT OF A PATENT**

[See section 7]

1. We,

- (a) M/S. IPCA LABORATORIES LIMITED
- (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India
- (c) Indian company incorporated under the Companies Act 1956

2. Hereby declare –

- (a) that we are in possession of an invention titled "**STABILIZED PHARMACEUTICAL ORAL SOLID DOSAGE COMPOSITIONS**"
- (b) that the Provisional Specification relating to this invention is filed with this application.
- (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

- (a) Thembalath, Ramchandran
- (b) 6/35, Prakash Co. Housing Society,  
Relief Road, Santacruz (West),  
Mumbai 400 054,  
Maharashtra, India
- (c) Indian National

  

- (a) Bansal, Yatish Kumar
- (b) Flat No. 3, Siras Villa,  
Plot No. 40, Sai Baba Park,  
Evershine Nagar, Malad (West)  
Mumbai 400 064  
Maharashtra, India
- (c) Indian National

3 84 1 जून 2003  
MUM 12003

17 APR 2003

DUPPLICATE

(a) **Singh, Veena**  
(b) 4/129, BHEL Officers Flats,  
Link Road, D. N. Nagar,  
Andheri (West)  
Mumbai 400 053  
Maharashtra, India  
(c) Indian National

(a) **Kotian, Reshma**  
(b) B/201, Shivchhaya,  
Opposite C. K. P. colony,  
Eksar Road, Borivali (West)  
Mumbai 400 091  
Maharashtra, India  
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

**GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI  
ROAD, KANDIVLI (EAST), MUMBAI – 400 101.**

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country  
declare that the applicant(s) herein are our assignee

**(Thembalath, Ramachandran)**

**(Bansal, Yatish Kumar)**

**(Singh, Veena)**

**(Kotian, Reshma)**

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.
8. Following are the attachment with the application:
  - (a) Provisional specification (3 copies)
  - (b) Statement and Undertaking on Form 3
  - (c) Fee Rs.5000/- in cheque bearing No. 637661 dated 16<sup>th</sup> April, 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

**Dated this the 16<sup>th</sup> day of April 2003**



**DR. GOPAKUMAR G. NAIR**  
Agent for the Applicant  
**GOPAKUMAR NAIR ASSOCIATES**  
Nair Baug, Akurli Road  
Kandivli (East), Mumbai – 400 101

To

**The Controller of Patents  
The Patent Office,  
At Mumbai.**

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**FORM 2**

**THE PATENTS ACT, 1970**  
(39 of 1970)

**PROVISIONAL SPECIFICATION**

[See section 10]

**"STABILIZED PHARMACEUTICAL ORAL SOLID DOSAGE COMPOSITIONS"**

- (a) **IPCA LABORATORIES LIMITED**
- (b) **48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India**
- (c) Indian Company incorporated under the Companies Act 1956

The following specification describes the nature of the invention and the manner in which it is to be performed:

DUPPLICATE

384/mum/2003  
17/04/2003

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## STABILIZED PHARMACEUTICAL ORAL SOLID DOSAGE COMPOSITIONS

### Technical Field

[001] The present invention relates to stabilized oral solid dosage compositions and process for formulating the same. More particularly, the present invention relates to a process for formulation of free flowing active pharmaceutical ingredients (API) using moisture barrier excipients. Further, this invention relates to coated granules of Paroxetine, the process for the preparation of such granules and oral solid dosage pharmaceutical compositions thereof.

### Background and Prior Art

[002] Many pharmaceutical active ingredients are sensitive to moisture and consequently solid compositions of these API's develop colour and spotting in spite of protective packing and storage. Dry granulation has been suggested in prior art as a means to eliminate use of water and thereby reduce effect of moisture on the product.

[003] One such moisture-sensitive active pharmaceutical ingredient is Paroxetine, a phenylpiperidine derivative, chemically described as (-)-trans-4-((4'-fluorophenyl)3-3 (3'4'-methylenedioxypyphenoxy)methyl)-piperidine, which is a selective serotonin reuptake inhibitor. Paroxetine is widely used worldwide in treatment of depression.

[004] US Patent 4,721,723 and EP 223403 discloses that the active substance in all commercial forms has been paroxetine hydrochloride and specifically with regard to tablets and other solid dosage forms, the active ingredient suggested for use has been Paroxetine hydrochloride hemihydrate.

[005] WO 95/16448 reveals that earlier commercial paroxetine hydrochloride hemihydrate tablets were made using a wet granulation process. Further, the commercial tablets exhibited a colour change i.e. the tablets developed a pink hue that is undesirable.

[006] Patent Application US2002065301 elaborates paroxetine salt compositions made with the aide of water by controlling the pH to 6.5 or less. These compositions have improved stability without significant coloration problems. The paroxetine salts include paroxetine hydrochloride salts but preferably use paroxetine sulfonate salts such as paroxetine methane sulfonate.

[007] US Patent 6,113,944 reveals an invention that provides paroxetine, which is formulated into tablets using a formulation process in which water is absent. Direct Compression technique has been used where paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients and compressed into tablets or by Dry granulation techniques as in US Patent 6,007,842 where paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients and compressed into large slugs or roller compacted into ribbon-like strands. The compacted material is then suitably milled

to produce a free flowing powder, which is then compressed into tablets. The excipients revealed in the patent include Dicalcium phosphate dihydrate, Microcrystalline cellulose, Sodium starch Glycollate and Magnesium stearate.

[008] In Patent application No.WO9958113 use of paroxetine is in amorphous form as well as in the form of a crystalline anhydrate, which is formulated into tablets under conditions such that there is no detectable conversion to hemihydrate during the tabletting process is described. Such conditions have been achieved by the use of essentially anhydrous or low moisture excipients such as dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosachharide sugars eg mannitol, disaccharide sugars eg lactitol, powdered cellulose, pregelatinised starch, microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and talc. Paroxetine hydrochloride anhydrate is mixed with the anhydrous or low moisture excipients and compressed using standard pharmaceutical procedures. As an additional aid to the protection of this product from the deleterious affects of moisture the tablets are film coated using hydrophobic coating materials such as glycetyl behenate using a hot melt coating technique.

[009] Patent Application No.WO9958116 describes the same API and excipients for a capsule formulation. Paroxetine hydrochloride anhydrate is mixed with the anhydrous or low moisture excipients and filled into cellulose capsule shell of intrinsically low moisture content (eg Shiono Qualicaps). The invention discloses that dibasic calcium phosphate anhydrous and polyglycolized glycerides can be used to form oral swallow capsules with paroxetine anhydrate without undesired conversion to hemihydrate during manufacturing process.

[010] Patent Application No.WO02102382 describes a process for preparing paroxetine hydrochloride from paroxetine base, which provides paroxetine hydrochloride substantially free of pink-colored compounds or an impurity identified by an HPLC RRT of about 1.5.

[011] US Patent. 5,955,475 describes an invention wherein paroxetine free base is advantageously formulated into pharmaceutical compositions when adsorbed on or absorbed by a solid carrier.

[012] Patent Application No.WO 9831365 elaborates a process for preparing a free flowing form of paroxetine hydrochloride, which comprises spray drying a solution of paroxetine hydrochloride. However no discussion appears in the patent regarding the paroxetine hydrochloride colouring problem.

[013] US Patent 6,168,805 discloses an invention that relates to a process for preparing solid, amorphous paroxetine comprising a) mixing paroxetine free base or its salt with water and a pharmaceutically acceptable polymer and b) drying to form a composition comprising amorphous paroxetine and polymer, eliminating the need for organic solvents common for the solvent process. The resultant amorphous solid paroxetine composition is free from crystalline form and yet has good handling properties, making it suitable for pharmaceutical use in the traditional tablet dosage form.

[014] In patent application no.WO0102393 complexes of paroxetine, as free base or salt, with cyclodextrin or a cyclodextrin derivative show a high chemical stability, an improved solubility in water and are suitable for the preparation of liquid or solid pharmaceutical compositions.

[015] In patent application WO9948499 Paroxetine free base is advantageously formulated into pharmaceutical compositions, when adsorbed or absorbed by a solid carrier. The composition of this invention is simply obtained by combining a solution of paroxetine with a suitable adsorbent or absorbent material and evaporating the solvent, for example by spray drying.

[016] US patent 6,503,927 describes a stable amorphous paroxetine hydrochloride composition employing an aqueous solvent medium containing an acidulant and polyvinylpyrrolidone and drying the resulting solid dispersion. The preferred compositions include amorphous paroxetine hydrochloride, polyvinylpyrrolidone and citric acid.

[017] The patent application no. WO9926625 provides pharmaceutical formulations of paroxetine, in which paroxetine is in solution in a solid, semi-solid or liquid carrier. The solutions are used to fill capsules, or self-supporting solid solutions are shaped into solid dosage forms such as tablets or pellets.

### **Summary**

[018] Coated granules of Paroxetine hydrochloride anhydride are disclosed, which are prepared using a solution of moisture barrier excipient and a nonionic surfactant in an organic solvent. Such granules are manufactured by preparing a semisolid mass of the API and the solution of moisture barrier coating, preparing strands of suitable diameter of the wet mass, drying the strands and finally milling to get granules of desired size. The granules of the API are then incorporated into oral solid dosage formulations of Paroxetine.

**Dated this the 16<sup>th</sup> day of April 2003**



**DR. GOPAKUMAR G. NAIR**  
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